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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/923,917 | 08/06/2001 | Alexander Varshavsky | GPCG-P01-017 | 9016 |

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| EXAMINER | |
|---|---|
| BURKHART, MICHAEL D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/923,917 | VARSHAVSKY ET AL. | |
| | Examiner | Art Unit | |
| | Michael D. Burkhart | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *9/13/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-114* is/are pending in the application.

4a) Of the above claim(s) *1-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,67,69,71,73,76,78,81-83,86-88,90,93,95,98-100,103-105,107,110 and 112* is/are rejected.

7)☒ Claim(s) *68,70,72, 74-75,77,79,80,84,85,89,91-92,94,96,97,101,102,106, 108-109,111,113 and 114* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/24/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group IX (claims 66-114) in the reply filed on 9/13/04 is acknowledged. In the reply applicants state that claims 20 and 66-68 were not addressed in the restriction, likely due to a typographical error. Upon consultation with Examiner Lambertson (author of the restriction) this was found to be the case. Claims 66-68 were intended to be in Group IX and claim 20 in Group VI and are hereby included in those Groups. The traversal is on the ground(s) that all Groups share certain technical features and suggest that a search for this common feature "ubiquitin-based fusion proteins" would potentially relate to all claims and not increase the search burden of the examiner. This is not found persuasive because a search of ubiquitin fusion proteins would yield a substantial volume of literature, most of which would not be relevant to the proteins, nucleic acids, or methods of the instant claims. To narrow the search to the relevant art requires a different search for each invention, evidenced by the different classification of some Groups and the differences between the Groups as detailed in the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

### *Priority*

This application, filed 8/6/2001, claims priority from application 60/223,411, filed 8/4/2000. The invention is granted a priority date of 8/4/2000.

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

### *Claim Objections*

Claims 68, 70, 72, 74-75, 77, 79-80, 84-85, 89, 91-92, 94, 96-97, 101-102, 106, 108-109, 111, and 113-114 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 66-67, 69, 71, 73, 76, 78, 81-83, 86-88, 90, 93, 95, 98-100, 103-105, 107, 110, and 112 are rejected under 35 U.S.C. 102(b) as being anticipated by Wittke et al (August 1st, 1999, cited by applicants, reference AS of the IDS). A telephone call from the USPTO Biotech library to the publisher of the Wittke reference established that the reference was released and publicly available on 8/1/1999. The instant claims are drawn to a method of characterizing

protein binding comprising the steps of: expressing a first nucleic acid in a ubiquitin-specific protease expressing cell wherein the nucleic acid encodes a target fusion protein comprising, from N- to C-terminus, P1-$C_{ub}$-X-RM; wherein P1 is the target protein, $C_{ub}$ is the C-terminal subdomain of ubiquitin, X is an amino acid selected from the group listed in the claim (destabilizing amino acids according to the N-end rule), and RM is an enzymatically active reporter moiety; expressing a second nucleic acid encoding segments P2 and $N_{ux}$, wherein P2 represents a member of a library and $N_{ux}$ is the amino-terminal subdomain of wild-type ubiquitin or a mutant that has reduced associating properties with the C-terminal subdomain; recovering a clone of a cell expressing both nucleic acids under conditions which select for the absence of the RM enzymatic activity; and characterizing the second nucleic acid encoding P2. RM may be selected from the group listed in claim 67, RM may be an active reporter moiety, the cell may be a eukaryotic cell, a fungal cell, or selected from the group in claim 76, the library of nucleic acids may comprise from 10-500 members and multiple members are not known to bind to P1, and Nux may contain point mutations at amino acids 3 or 13. Claims 82-83, 86, 87-88, 93, 95, 98-100, 103-105, 110, and 112 present the same invention in the form of kits that merely add instructions. The instructions state that a target sequence is to be inserted as P1 and library members are to be inserted as P2.

Wittke et al teach the expression of two nucleic acids in the ubiquitin-specific protease expressing yeast *S. cerevisiae*. The first nucleic acid comprises one of several target proteins (i.e. P1) linked to $C_{ub}$-RUra3. In this case R represents an arginine residue (and thus an "X" amino acid from above) and Ura3p the enzyme of the same name which is active in this case (see pg 2521 and Figs. 1 and 2). The second nucleic acid comprises one of thirteen yeast

proteins (P2) linked to $N_{ub}$ or mutants $N_{ua}$ or $N_{ug}$ (Figs. 1 and 2), some of which are not known to bind to the P1 target (Sec63p). Both $N_{ub}$ mutants were point mutations at position 13. Cells expressing both nucleic acids were selected under conditions which favor the absence of Ura3p (i.e. in the presence of 5-FOA) in Table 1, and the second nucleic acid (P2) was characterized for the ability of its encoded protein to bind the target of P1 (Table 1 and Fig. 5). The reference itself represents printed material (instructions) that teach the insertion of a target (Sec63p in this case) into the $C_{ub}$-X-RM construct and a library of nucleic acids into the $N_{ub}$ construct (the proteins from Fig. 2). The authors also state that the features of this assay make it possible to select for binding partners of "..any other CRUp-labeled protein." (page 2528, second column third paragraph).

Claims 66-67, 69, 71, 73, 76, 81-83, 86-88, 90, 93, 98-100, 103-105, 107, and 110 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnsson et al (in The Yeast Two-Hybrid System, 1997). The claims are as described above.

Johnsson et al teach a screening method for "..genes whose products interact with a protein of interest.." comprising expression of two nucleic acids in the ubiquitin-specific protease expressing yeast *S. cerevisiae* (pg. 328 paragraph labeled "4"). The first nucleic acid comprises the protein of interest (i.e. P1) linked to $C_{ub}$-d-R. In this case "d" represents a destabilizing residue (arginine and leucine are listed as examples) and R the reporter, of which Ura3p is listed as an example (pg. 328 paragraph labeled "4"). The second nucleic acid comprises an expression library of nucleic acids (P2) linked to a mutant $N_{ub}$ moiety. $N_{ub}$ mutants include point mutations at position 13 (pg. 321, second paragraph). An expression library, by definition, represents cDNAs of genes expressed by a cell, and therefore represents a multitude of nucleic acids, of

which multiple members are not known to bind to any given target. Cells expressing both nucleic acids can be selected for the "..conditionally active degradation.. " (i.e. the absence) of Ura3p. In doing so, the second nucleic acid (P2) has therefore been characterized for the ability of its encoded protein to bind the target of P1. The reference itself represents printed material (instructions) that teach the insertion of a target into the $C_{ub}$-d-R construct and insertion of a library of nucleic acids into the $N_{ub}$ construct.

***Conclusion***

No claims are allowed.

Other relevant prior art is exemplified by Dunnwald et al (Mol. Biol. Cell, 1999) Stagljar et al (PNAS, 1998, cited by applicants in the IDS) and Johnsson et al (U.S. Patents 5,503,977 and 5,585,245, cited by applicants in the IDS). All of the references teach the method and ubiquitin constructs of the instant invention, but none teach modification of the reporter moiety such that its N-terminal amino acid is not methionine (i.e. the "X" of the P1-$C_{ub}$-X-RM construct). The above references teach the reporter to be inactive until protein association and cleavage from $C_{ub}$, upon which the reporter becomes active. In the instant invention, the reporter is active until protein association and cleavage from $C_{ub}$, then is targeted for degradation (becomes inactive) courtesy of the addition of the N-terminal amino acid X.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER